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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,217	CHANG, CHIA NING (SOPHIA)	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-10 are pending in the present application.

Applicant's election of the invention of Group I (claims 1-8) in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 9-10 are withdrawn from further consideration because they are drawn to a non-elected invention.

Claims 1-8 are examined on the merits herein.

Specification

In the Brief Description of the Drawings Section, Fig. 2, 3, 4, 5, 7, 8, 9, 13, 14, 15, 16 are referred. However, Fig. 2A-B, 3A-B, 4A-B, 5A-D, 7A-C, 8A-B, 9A-C, 13A-B, 14A-B, 15A-B and 16A-C are submitted. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of enhancing new bone formation in a subject, comprising:

a) obtaining a plurality of bone marrow stromal cells (MSCs) from the subject;

b) transducing the MSCs of step a) with a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter to generate BMP-2 protein producing MSCs; and

c) implanting the BMP-2 protein producing MSCs at a site requiring new bone formation in said subject;

does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are drawn to a method of treating a bone or other tissue defect comprising: (a) obtaining a plurality of MSCs from a subject; (b) transferring a BMP-2 gene to the MSCs to form BMP-2 protein producing MSCs; and (c) implanting the protein producing MSCs to a site on the subject; the same method with various limitations recited in the dependent claims.

The specification teaches by exemplification showing the preparation of autologous bone marrow stromal cells (MSCs) from iliac crests of mini pigs, which are transfected with a recombinant adenovirus expressing human BMP-2 (MSCs transfected with adv-BMP-2). In an experimental model of mini-pigs having critical size cranial bone defects, upon implantation of the autologous transfected MSCs in the polymer Pancogene S (collagen type I) at the bone defective site, a significant increase of bone formation was observed at 3 months, indicating that the polymer Pancogene S/MSCs transfected with adv-BMP-2 can enhance the bony healing of critical size craniofacial defect. Similarly, a near-complete defect repair at the defective maxillary bone sites was achieved 3 months after implantation of the autologous transfected MSCs in the polymer Pancogene S at the generated defective sites in minipigs. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

The instant claims encompass a method of treating a defect or injury to the bone, cartilage, muscle, adipose or other fibrous tissues upon implantation of autologous BMP-2 protein producing bone marrow stromal cells to a subject. Apart from the exemplification showing that a significant and enhanced bone formation occurs at a bony defective site using autologous MSCs transfected with a recombinant adenovirus expressing human BMP-2, the instant specification fails to provide sufficient guidance for a skilled artisan on how to repair a defect or injury at any non-bony tissues, e.g., cartilage, muscle, adipose

tissues. Moreover, there is no evidence of record indicating or suggesting that the expression of BMP-2 in MSCs could induce the transfected bone marrow stromal cells to differentiate into cells with phenotypes other than osteoblasts *in vitro* or *in vivo*, let alone for yielding any therapeutic effects at non-bony defective sites. Furthermore, Lou et al. (J. Orthopaedic Research 17:43-50, 1999) and Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001) teach that adenovirus-mediated human BMP-2 gene transfer induces mesenchymal progenitor C3H/10T cells and mesenchymal stem cells to proliferate and differentiate into osteoblast phenotype that result only in induced bone formation *in vitro* and *in vivo* (see abstract). Since the prior art at the filing date of the present application does not provide guidance on the aforementioned issues, it is incumbent upon the instant specification to do so. In the absence of sufficient guidance provided by the present application, it would have required undue experimentation for one skilled in the art to make and use the full scope of the presently claimed methods. Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The instant claims encompass the implantation of autologous BMP-2 producing MSCs at any site on the subject (not necessarily at the defective site)

for treating any defect or any injury to the bone, cartilage, muscle, adipose or other fibrous tissues. The instant specification is not enabled for such a broadly claimed invention. The present disclosure offers no guidance for a skilled artisan on to target the autologous BMP-2 producing MSCs to any defective or injury sites in a subject, so that the MSCs can proliferate and differentiate into sufficient number of appropriate cells to yield the desired therapeutic effects. For example, it is unclear how an implantation of the transfected MSCs cells on a limb or in a breast tissue would result in any therapeutic effects for treating a defective or injury in a femur? Furthermore, it is well known in the gene therapy art that transgene expression *in vivo* is very transient. For examples, Palmer et al. (Proc. Natl. Acad. Sci. 88:1330-1334, 1991) demonstrated that the *in vivo* expression of human factor IX by transplanted syngeneic recombinant fibroblasts was transient and vanished 1-5 weeks post-transplantation. Riddell et al. (Nature Med. 2:216-223, 1996) reported that five out of six patients seropositive for human immunodeficiency virus developed cytotoxic T-lymphocytes responses specific to a novel protein and eliminated infused autologous CD8+ HIV-specific cytotoxic T cells transduced with a novel fusion suicide gene (See abstract). Thus, it is unclear whether the recombinant BMP-2 produced by the implanted autologous MSCs could be delivered to the targeted defective or injury site at a sufficient amount to produce any therapeutic effects. Additionally, it is known that the half-life of recombinant human BMP-2 is very short and that a large amount of BMP-2 protein is often required to stimulate significant new bone formation *in vivo* as already recognized by Applicants (see page 2, lines 22-24). Therefore, with the

lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art and gene therapy art in general, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and its dependent claims, it is unclear what is encompassed by the phrase "an adenovirus mediated human BMP-2 gene". Should Applicants mean a recombinant adenovirus expressing a human BMP-2 protein or a recombinant adenovirus comprising a DNA sequence encoding a human BMP-2 protein, then recite as such. Otherwise, the metes and bounds of the claims are not clearly determined.

In claim 5 and its dependent claims, there is no connection or relationship between the steps of a) to c) with treating a bone or other tissue defect as recited in the preamble of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Moutsatsos et al. (WO99/11664).

Claims 1-2 are drawn to a pharmaceutical composition comprising a plurality of bone marrow stromal cells transfected with a recombinant adenovirus expressing human BMP-2, and a pharmaceutically acceptable polymer; the same composition wherein the polymer is alginate or collagen.

Moutsatsos et al. disclose the preparation of cells (cell lines or primary cells including bone marrow stromal cells) transformed with a recombinant vector (including viral vectors such as adenovirus and retrovirus) expressing one or more bone morphogenetic proteins (BMPs, including human BMP-2) or growth and differentiating factors (GDSs) for regeneration of bone formation *in vivo* (see example 14, pages 41-50). Moutsatsos et al. also teach that the recombinant cells can be administered in combination with an appropriate matrix for supporting the composition, and this matrix can be in the form of biocompatible

matrix biomaterials (a pharmaceutically acceptable polymer) including polylactic acid, polyanhydrides, calscium sulfate, bone, dermal collagen, hydroxyappatite, aluminates, pure proteins or extracellular matrix components and others (line 32 on page 6 continues to line 27 on page 7).

Accordingly, Moutsatsos et al. (WO99/11664) anticipate the instant claims.

Claims 1-2, 4-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Riew et al. (Calcif. Tissue Int. 63:357-360, 1998).

Riew et al. teach the preparation and transduction of rabbit bone marrow mesenchymal stem cells isolated from bone marrow cells, with a recombinant adenoviral vector expressing human BMP-2 for transplantation in a rabbit spinal fusion model (see Materials and Methods on page 358). Riew et al. further teach that the transfected cells were harvested and resuspended in collagen solution (Pancogene S) at 3x 10^6 cells/ml for autologous implantation into the L5/L6 interspace of rabbits from which the bone marrow cells were harvested 4 weeks earlier (page 358, under sections titled "Human BMP-2 protein expression in MSC cells" and "Rabbit spine fusion model"). Riew et al. further demonstrate that new bone formation occurs at the site of autologous implantation of Adv-BMP2 transduced mesenchymal stem cells in one of the treated animals (Figs. 2-4). Since a plurality of bone marrow stromal cells transformed or transfected with a recombinant adenovirus expressing human BMP-2 of the instant claims encompass a population of bone marrow mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 taught by Riew et al.,

coupled with the same method steps and a treated rabbit as a subject, the reference anticipates the instant claims.

Claims 1-2, 4-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001).

Cheng et al. teach the preparation and transduction of rabbit bone marrow mesenchymal stem cells isolated from bone marrow cells, with a recombinant adenoviral vector expressing human BMP-2 for transplantation in a rabbit spine fusion model (see Materials and Methods on page 88). Cheng et al. further teach that the transfected cells were harvested and resuspended in collagen solution (Pancogene S) at 3x 10^6 cells/ml for autologous implantation into the L5/L6 interspace of rabbits from which the bone marrow cells were harvested 4 weeks earlier (page 88, col. 2, under sections titled "Transducing rabbit bone marrow mesenchymal stem cells with Adv-BMP2" and "Rabbit spine fusion model"). Cheng et al. further demonstrate that new bone formation occurs at the site of autologous implantation of Adv-BMP2 transduced mesenchymal stem cells. Since a plurality of bone marrow stromal cells transformed or transfected with a recombinant adenovirus expressing human BMP-2 of the instant claims encompass a population of bone marrow mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 taught by Cheng et al., coupled with the same method steps and a treated rabbit as a subject, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moutsatsos et al. (WO99/11664) in view of Riew et al. (Calcif. Tissue Int. 63:357-360, 1998) or.Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001).

Moutsatsos et al. disclose the preparation of cells (cell lines or primary cells including bone marrow stromal cells) transformed with a recombinant vector (including viral vectors such as adenovirus and retrovirus) expressing one or more bone morphogenetic proteins (BMPs, including human BMP-2) or growth and differentiating factors (GDSs) for regeneration of bone formation via *in vivo*

or *ex vivo* gene therapy (see example 14, pages 41-50). Moutsatsos et al. also teach that the recombinant cells can be administered in combination with an appropriate matrix for supporting the composition, and this matrix can be in the form of biocompatible matrix biomaterials (a pharmaceutically acceptable polymer) including polylactic acid, polyanhydrides, calscium sulfate, bone, dermal collagen, hydroxyappatite, aluminates, pure proteins or extracellular matrix components and others (line 32 on page 6 continues to line 27 on page 7). Moutsatsos et al. do not specifically teach an autologous implantation method using a plurality of bone marrow stromal cells transformed or transfected with a recombinant vector expressing BMP-2 from a subject even though Moutsatsos et al. teach the implantation of collagen gels containing marrow stromal cells infected with a recombinant adenovirus expressing human BMP-2 into syngeneic mice (see example 14). Moutsatsos et al. also do not teach the make and use of a composition comprising bone marrow stromal cells transfected with a recombinant adenovirus expressing human BMP-2 at a concentration of 50 x 10^6 cells per ml of a pharmaceutically acceptable polymer.

At the effective filing date of the present application, both Riew et al. and Cheng et al. already teach the preparation and transduction of autologous rabbit bone marrow mesenchymal stem cells isolated from bone marrow cells, with a recombinant adenoviral vector expressing human BMP-2 for transplantation in a rabbit spinal fusion model (see Materials and Methods section). Both Riew et al. and Cheng et al. further teach that the transfected cells were harvested and resuspended in collagen solution (Pancogene S) at 3x 10^6 cells/ml for autologous

implantation into the L5/L6 interspace of rabbits from which the bone marrow cells were harvested 4 weeks earlier. Both Riew et al. and Cheng et al. further demonstrate successfully that new bone formation occurs at the site of autologous implantation of Adv-BMP2 transduced mesenchymal stem cells in the treated animals.

Accordingly, it would have been obvious and within the scope of skill for an ordinary skill artisan to modify the composition and method taught by Moutsatsos et al. (WO99/11664) by using harvested autologous mesenchymal stem cells from bone marrow or bone marrow cells, that have been transfected with a recombinant vector expressing human BMP-2 for induction of bone formation at a desired site in a subject in need thereof, in light of the teachings of Riew et al. or Cheng et al. It would also have been obvious that the transfected BMP-2 protein producing mesenchymal stem cells can be formulated in Pancogen S polymer, an appropriate matrix that has been utilized by both Riew et al. and Cheng et al. for supporting the transfected cells for bone induction *in vivo*. Additionally, it would also have been obvious for one of ordinary skilled artisan to utilize various concentrations of the transfected mesenchymal stem cells in a collagen solution, including the concentration of 50×10^6 transfected cells per ml of a pharmaceutically acceptable polymer for optimizing the desired degree of bone formation *in vivo*.

An ordinary skilled artisan would have been motivated to make the above modifications because an increased in the concentration of implanted mesenchymal stem cells transfected with a recombinant adenovirus expressing

human BMP-2 would result in an increased in differentiated osteoblasts as well as the amount of secreted human BMP-2 at the implanted site to increase bone formation as required. Furthermore, one of ordinary skilled artisan would have been motivated to use autologous mesenchymal stem cells from bone marrow or bone marrow cells, that have been transfected with a recombinant vector expressing human BMP-2 for induction of bone formation at a desired site in a subject in need thereof to minimize any adverse host immune responses against the transplanted cells, which is recognized by Moutsatsos for the teaching of implantation of collagen gels containing marrow stromal cells infected with a recombinant adenovirus expressing human BMP-2 into syngeneic mice (see example 14).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 3, 5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Riew et al. (Calcif. Tissue Int. 63:357-360, 1998) or Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001).

Both Riew et al. and Cheng et al. teach the preparation and transduction of rabbit bone marrow mesenchymal stem cells isolated from bone marrow cells, with a recombinant adenoviral vector expressing human BMP-2 in a rabbit spinal fusion model (see Materials and Methods section). Both Riew et al. and Cheng et al. further teach that the transfected cells were harvested and resuspended in collagen solution (Pancogene S) at 3x 10^6 cells/ml for autologous implantation

into the L5/L6 interspace of rabbits from which the bone marrow cells were harvested 4 weeks earlier. Both Riew et al. and Cheng et al. further demonstrate successfully that new bone formation occurs at the site of autologous implantation of Adv-BMP2 transduced mesenchymal stem cells. It is noted that a plurality of bone marrow stromal cells transformed or transfected with a recombinant adenovirus expressing human BMP-2 of the instant claims encompass a population of bone marrow mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 taught by both Riew et al. and Cheng et al. Neither Riew et al. nor Cheng et al. teach a composition wherein the bone marrow stromal cells are present in a concentration of about 50 x 10^6 per ml of a pharmaceutically acceptable polymer, and a method of using the same.

However, at the effective filing date of the present application it would have been obvious and within the scope of skill for an ordinary skill artisan to modify the composition and the method taught by Riew et al. or Cheng et al. by using a higher concentration of the transfected mesenchymal stem cells in a collagen solution, including the concentration of 50 x 10^6 transfected cells per ml of a pharmaceutically acceptable polymer, for optimization the desired degree of bone formation *in vivo*.

An ordinary skilled artisan would have been motivated to make the above modification because an increased in the concentration of implanted mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 would result in an increased in differentiated osteoblasts as well

as the amount of secreted human BMP-2 at the implanted site to increase bone formation.

Therefore, the claimed invention as a whole was *prima facie* obvious.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

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